Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2009 December ; 18(12): 3321–3333. doi:
10.1158/1055-9965.EPI-09-0925.

Cigarette Filter-based Assays as Proxies for Toxicant Exposure and Smoking Behavior A Literature Review

John L. Pauly¹, Richard J. O'Connor², Geraldine M. Paszkiewicz¹, K. Michael Cummings²,
Mirjana V. Djordjevic³, and Peter G. Shields⁴

¹ Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY 14263

² Department of Health Behavior, Roswell Park Cancer Institute, Buffalo, NY 14263

³ Tobacco Control Research Branch, National Cancer Institute, Rockville, MD 20892

⁴ Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC 20057

Abstract

Background—Cigarettes are being marketed with filters that differ in composition and design. The filters have different toxicant trapping efficiency and smoking stains reflect variations in smoking behavior. Presented herein are the results of a structured literature review that was performed to identify cigarette filter-based assays that may serve as proxies for mouth-level exposure and assessing smoking methods.

Methods—A search of the published scientific literature and internal tobacco company documents from 1954 to 2009 was performed.

Results—The literature search identified diverse schemes for assessing cigarette filters, including visual inspection and digital imaging of smoked-stained spent filters, and quantitative determinations for total particulate matter (TPM), nicotine, and solanesol. The results also showed that: (a) there is sufficient data to link filter-based chemical measures to standardized smoking machine-measured yields of tar and nicotine; (b) TPM eluted from filters or in chemical digest of filters can be used to estimate the efficiency of the filter for trapping smoke solids; (c) visual and digital inspection of spent filters are useful as indicators of variations in smoking behaviors; and (d) there is a correlation between solanesol and nicotine measured in filters and exposure biomarkers in smokers.

Conclusions—The cigarette filter may prove useful in estimating smoking behaviors such as filter vent blocking and puffing intensity, and may have utility as proxy measures of mouth-level smoke exposure in clinical trials. Additional investigations are needed to compare the different proposed assay schemes and the assay results with measurements of human biomarker assays of smoke exposure.

Keywords

cigarette; filter; tar; nicotine; tobacco

Correspondence: John L. Pauly, Ph. D. Associate Member, Department of Immunology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, Phone: (716) 845-8538, Fax: (716) 845-1322, john.pauly@roswellpark.org.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Introduction

The filtered cigarette gained prominence in response to the health fears surrounding smoking beginning in the mid-1950s, accompanied by extensive advertisements emphasizing safety (1,2). The history of cigarette filters as well as diverse filter designs and components have been detailed in research papers and US Patents. A chronological overview of cigarette filters and selected reports of studies in which filters have been explored as proxies of toxicant exposure and smoking behavior is presented in Table 1.

Today, filtered cigarettes account for 99% of US cigarette sales (3), and the filter is a continuing target of product innovation by the cigarette industry as reflected in patents and new product introductions. For example, selective filtration technologies have been recently introduced and marketed on novel cigarettes that are being promoted as potential reduced exposure products (PREPs), such as B&W's *Advance*, Vector Tobacco's *Omni*, and Philip Morris' Marlboro *UltraSmooth* (4,5). Cigarette filter materials (e.g., cellulose acetate and charcoal) and filter designs (filter ventilation and multi-segment filters), and the effects of different filters on the mechanical and chemical retention of mainstream smoke components have been reviewed previously (6).

The introduction of PREPs has led to a growth in diverse methodologies for assessing smokers' exposure to various smoke constituents. Also, different schemes have been proposed for measuring how a person actually smokes the product; this is known as smoking topography (1).

Determining the exposure reduction of a particular PREPs relative to conventional cigarettes is complex, involving measurement of both smoke yield and behavior (7,8). This represents an important lesson from the Regular/Full flavor to Light/Low-tar cigarette experience, where it was presumed that changes in cigarette tar yields would lead to changes in exposure. We now know that smoker-product interactions are extremely important in determining exposure to smoke constituents, a phenomenon known as compensation, where smokers adjust their smoking behavior to titrate their nicotine intake (9). More recently it has been established that biomarkers of tobacco smoke exposure show that levels of nicotine and carcinogen metabolites are no different between Full-flavor, Light and Ultra light cigarette categories (10–13).

It is widely accepted that human exposure cannot be fully defined using smoke emissions derived from smoking machines (9,14). By way of example, Hammond and co-workers undertook an investigation to compare measures of smoke volume and nicotine uptake among human smokers against the puffing variables and nicotine yields generated by five different machine smoking regimens (15). The results of the study documented that none of the four machine smoking regimens adequately represented human smoking behavior, nor did they generate yields associated with human measures of nicotine uptake. This can be carried to measures of biological effect. Anderson and co-workers (16) have reported the results of a study to define the influence of cigarette consumption and smoking machine yields of tar and nicotine on the nicotine uptake and oral mucosal lesions of smokers. They concluded that the nicotine uptake was significantly correlated to the number of cigarettes smoked per day but not to the smoking machine yields of tar and nicotine per cigarette.

There is a tradition in the social sciences of utilizing proxy measures to estimate other, harder-to-measure parameters (17). While not a true substitute, the proxy measures can provide useful information, often in a more easily accessible form. It may be practical, for example, to use the cigarette filter as a potential proxy for exposure to tobacco smoke constituents. Because smoke is drawn into the filter by the smoker's puff, what exits the proximal (mouth) end of the filter should be proportional to what entered the distal (tobacco) end of the filter. In a ventilated filter, air drawn through the vents also enters the equation. Air from the vents changes the

smoke flow patterns but does not alter the basic reality that what comes out has to be a function of what went in.

A number of research groups have explored various approaches, to be detailed below, for using the material trapped by the filter as an indicator of smoke exposure. In addition, several lines of investigation have used spent filters of smoked cigarettes to identify characteristics of smoker behavior (e.g., puff intensity and filter vent blocking).

For the assessment of PREPs, it is important to clarify whether a filter-based assay can be used to assess modern PREPs, such as B&W's *Advance* and Philip Morris' Marlboro *UltraSmooth*. The filter is an ongoing focus of active tobacco industry research and development. Indeed, a search of 'cigarette filter' in Google Patents database returned 89 US patents issued to Philip Morris, 44 patents to R. J. Reynolds Tobacco Company, and three patents to Lorillard Tobacco Company; all patents had been issued since Year 2000.

Reported herein are the results of a structured review of the literature that was performed to: (a) evaluate filter-based assays to measure filter trapping efficiency and variations in smoking behavior, (b) assess the advantages and disadvantages of the different technologies; (c) determine whether such assays can act as proxies for exposure to tobacco smoke, and (d) identify the research gaps needed to be able to use cigarette filter-based assays to assess human exposure.

Methods

We reviewed scientific papers published in peer-review journals; meeting abstracts, slide lectures, and poster presentations, as well as tobacco industry internal documents. A search of the scientific literature was performed from 1957 through 2009. Peer-reviewed papers were sought in databases of *PubMed*TM (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed>) and *Scopus*TM (<http://info.scopus.com/etc/citationtracker/>). Topic-specific writings were also sought in US Patents; these were searched using the database at GoogleTM (<http://www.google.com/patents>) and the United States Patent and Trademark Office (<http://www.uspto.gov/>). Tobacco industry documents, surrendered as a result of litigation, were retrieved from Tobacco Documents OnlineTM (<http://tobaccodocuments.org/>) and the Legacy Tobacco Documents Library (<http://legacy.library.ucsf.edu/>).

Company databases were also searched, including, by way of example, sites for Philip Morris USA (<http://philipmorrisusa.com/en/cms/Home/default.aspx>), RJ Reynolds Tobacco Company (<http://www.rjrt.com/>) and the British American Tobacco Company (<http://www.bat.com/>).

Additional writings were sought in meeting abstracts of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) at <http://www.coresta.org/>. In addition, searches of the tobacco science publications *Beitrag zur Tabakforschung (Contributions to Tobacco Research)* (<http://www.beitraege-bti.de/nxt/gateway.dll?f=templates&fn=default.htm&vid=btft:btfti>), *Recent Advances in Tobacco Science*, and *Tobacco Science Research Conference* abstracts were conducted.

Search of the databases were made using keywords and short-string phrases and basic Boolean operators. Keywords and phrases, either singularly or in combination, and included, by way of example: *filter*, *cigarette*, *tar*, *nicotine*, *filtration efficiency*, *staining*, *color*, *stain pattern* and other subject-specific terms. Efforts were made to avoid any bias. All papers published in peer reviewed journals were included. All recovered documents were reviewed and examined. Notable, topic-specific abstracts, which had not been subsequently published as a paper, were

also included. References cited in the publications were used to identify additional papers not recovered in keyword searches. Each paper retrieved was read critically for soundness of methodology (e.g., study design, analytic methodology, benchmarks and reproducibility).

Results

Results of literature search of cigarette filter-based assays

Table 1 presents a chronological listing of milestones for filter development. Included in this tabulation are key papers that described cigarette filter-based assays as proxies for smoking behavior and exposure (18–89). The literature source of the 70 papers is presented in Table 2.

Our analysis of the literature identified different methods using spent cigarette filters as proxies for measuring smoking behavior and exposure to smoke constituents. These methods included (1) visual and (2) digital imaging of the filter cut surface, and the analyses of filters for (3) particulates, (4) nicotine, and/or (5) solanesol. Findings relevant to each of these five methods are reviewed below.

Visual Inspection and Imaging

Analytical Methods Based on Visual Inspection of the Filter—Among the simplest methods for assessing smoke emissions and exposure is to visually examine the intensity and pattern of the tar stain (Figure 1). This is used to assess how smokers block the vent holes on filters. The vents are generally located 12 to 15 mm from the mouth end of the filter, and are organized in a ring around the filter. When a filtered cigarette is smoked, smoke is drawn through the filter and some particulate matter is trapped by filter material such as on cellulose acetate fibers. Over the course of smoking a cigarette, the filter becomes ‘stained’ a brownish color due to the accumulation of smoke deposits. When the fingers of the smoker block the vent holes, the staining of the cut surface of the filter takes the shape of a “bull’s-eye” pattern (Figure 1).

Kozlowski and colleagues first presented the concept of utilizing the filter observations in semi-quantitative measurements, noticing that as more vents were blocked, “*observable smoke deposits increase on the proximal [smoker] side of the perforations, and staining spreads toward the sides of the filter*” (32). The stain appears as a central tar stain surrounded by a ring of unstained filter, the size which varies directly with the level of ventilation. The higher the level of ventilation, the more unstained area is found. Baker and Lewis (51) reported that the filter stain pattern depends on manufacturing variables such as degree of ventilation, number of vent holes, size of vent holes, number of rows of holes, and depth to which the vents extend into the filter. Thus, this assay is useful to determine the amount of vent hole blocking by smokers, which can vary from smoker to smoker and affect exposure (32). If one were to block some ventilation holes, the air flow through the outer edge would be reduced. Further, if one were to cover all of the holes, the stain would be uniform. Figure 1 also illustrates the filter stain pattern on the cut-end of a cigarette that has been smoked in which the vents had or had not been blocked.

Visualizing filter stain patterns is only semi-quantitative because it relies on an observers estimate for the percentage of the outer edge of the filter that was stained. Several studies have investigated the reliability and validity of the technique on Ultra Light and Light cigarette brands (33). Lombardo and colleagues (34) performed the first controlled experimental studies of the stain pattern technique, finding that ratings for unblocked (accuracy, 79%) and completely blocked (90%) butts were equally accurate and better than for partially-blocked butts (52%). When partial and full block were combined, 90% of partially blocked butts were

categorized as blocked. The authors note that the rate of false-positives was twice as great as the rate of false-negatives.

Kozlowski *et al.* (33) examined filters collected from smokers at shopping malls and applied a three-level rating system: (i) no stain at the outside edge or stain <3 mm (not blocked), (ii) light-to-moderate stain around outside (partially blocked), and (iii) uniform stain (fully blocked). Three independent raters were used and scores were derived by averaging across raters: 58% of butts showed some blocking, 42% showed no blocking and 19% of butts showed full blocking. No differences in blocking frequency were seen as a function of tar yield (i.e., blocking was as likely with 4 mg cigarettes as with 1 mg cigarettes). Inter-rater correlations ($r = 0.86, 0.86, \text{ and } 0.91$) were high, as was concordance ($r = 0.95$).

Pillitteri and colleagues (42) examined ratings of stain patterns and concluded that the method “*is best suited to detect the presence versus absence of vent-blocking rather than the extent of vent-blocking*” (p.407). There are examples of utilizing this method for qualitative assessment of filter vent blocking in human studies (90,⁹¹).

Sweeney (46) assessed reliability and accuracy for visualizing butt staining patterns and found that the test-retest and inter-rater reliabilities were high ($r = >0.90$), and the sensitivity and specificity were good ($r \geq 0.80$) for a variety of Light and Ultra Light brands. Prignot and Jamart (61) also have reproduced the accuracy of stain pattern assessment of vent blocking in a sample of butts collected from a Belgian hospital. The published studies reviewed here indicate that a visual stain pattern test can be useful to identify cases when cigarettes go unblocked and can reliably distinguish between the presence and absence of blocking. However, the technique cannot discriminate degrees of blocking (i.e., number of puffs blocked or amount of ventilation occluded by lips or fingers). To this end, the technique is sufficient to estimate the prevalence of any degree of vent-blocking in the general public, but is likely unsuitable to estimate the increase in exposure received by smokers who block vents.

O'Connor and colleagues have recently extended and automated this assay to take advantage of digital image analysis technology (63). The system involves taking a color digital picture of the mouth end of the cigarette butt and segmenting it into edge and center portions. The mean color value is then calculated for each region and the ratio of the two serves as an index of blocking. Two studies evaluated the effectiveness of three-color measures (i.e., hue, saturation, and value) at discriminating whether at least 50% blocking had occurred. In study #1, saturation showed perfect discrimination between unblocked Carlton butts and butts with at least 50% of the vents blocked during syringe smoking. In study #2, saturation showed 95% accuracy at identifying Marlboro *Ultra Light* butts with at least four puffs blocked by smokers' lips. The results indicated that the pattern of color saturation was related to vent blocking. Since this paper, the investigator has adopted the same international standard color system used by Rickert and colleagues (43,⁵⁶), but the basic principles remain consistent. This improved visualizing method also will need to be validated against a human biomarker exposure assessment.

Estimation of smoking intensity—In 1980 Kozlowski proposed a visual color scale that was used by smokers to estimate the number of puffs taken on the cigarette (32). In this technique, spent cigarette butts were compared to three standardized colors placed along an 11-point scale. Butts had been generated by syringe-smoking and had between 5 and 16 puffs (35 cc) taken from the cigarettes. Overall, the correlation between ratings and puff number was good ($r = 0.97$) (32).

This subjective technique was linked to filter nicotine by Devitt *et al.* (36) who reported that color ratings by smokers correlated well with analytical values ($r \sim 0.88$). Husset and colleagues

(50) noted a correlation between cigarette butt stain color and the estimated amount of tar yield on a smoking machine for 22 French cigarette brands (“full flavor”, “lights”, “super lights” and “ultra lights”). Color measures taken from these cigarettes were used to create a color scale. The authors concluded that “*There is a clear relation between the amount of tar and the stain diameter as well as its color intensity.*”

In 1994, Rickert and coworkers (43) extended the studies of Kozlowski et al (39) obtaining measures of stain color (i.e., hue, lightness, and chroma) from particulate matter collected on Cambridge pads by or trapped by filters by reflectance spectrometry when the cigarettes were smoked on a smoking machine. The amount of tar was best predicted by stain lightness (i.e., the degree of grayness). This relationship was linear when the data were converted to a logarithmic scale, and predicted tar values to within 0.5 mg (43). Rickert and colleagues (56) have continued their work on tar color and smoke toxicant yields. Using a different color determining system (i.e., MacBeth Color-Eye 2020+ spectrophotometer), they have related filter stain color to selected smoke constituents such as nicotine, total particulate matter, tobacco-specific *N'*-nitrosamines (e.g., NNK), and styrene. Rickert and colleagues (56) also noted that the “*a* dimension*”, which defines the relative amount of red or green in the image, was most sensitive to changes in smoking intensity.

O'Connor and colleagues (63,⁸⁰) have applied the earlier work of Kozlowski (32,^{33,39,41}) and Rickert (43) to examine the relationship between staining intensity and smoking topography. In a 2007-paper, O'Connor and co-workers found that total puff volume per cigarette correlated −0.71 with cigarette staining intensity (80). In multivariate modeling, central staining, indicating the major path of smoke flow, and the ratio of edge to center staining. This showed that the peripheral staining associated with vent blocking could be used to predict >80% of variance in total puff volume. Furthermore, Strasser *et al.* (58) and O'Connor *et al.* (63) demonstrated that changes in staining scores correlated with changes in smoking topography, providing evidence that staining intensity could be indicative of smoking behavior, and could be useful to examine changes in smoking behavior.

Visual inspection techniques, including digital imaging, appear to hold promise for assessing behavioral features of smoking, such as filter vent blocking, total puff volume, and number of puffs taken. The rater-based stain pattern assessment can judge only the presence or absence of vent blocking, but is unsuited for assessing extent of vent blocking (i.e., proportion of vents blocked). It is hoped that the digital image assessment system might improve upon this limitation with further development. Consistent with early findings that visually assessed stain color was associated with puff number, later work using standardized color analysis shows promise for estimating puff number and total smoke volume drawn through a filter, though further developmental work is necessary. Additional research is needed to validate this method of assessing human exposure through biomarker studies.

Tar Elution and Fluorescence

Cigarette filter efficiency assayed using eluted tar—Filter efficiency is a central concept for the “*functionality of filters.*” A 1980 internal Philip Morris dictionary of tobacco terms defined this term as “*the percentage of the incoming smoke or smoke component that is removed by a filter.*” (92). Therefore, measuring efficiency can be an important consideration in terms of the utility of filters as proxy measures of smoking behavior or smoke exposure. One simple method for measuring the smoke solid-trapping efficiency of filters has been to compare the weight of filters before and after smoking; this has been described as the gravimetric method (20).

A number of fluorescent-based methods have been applied to assess filter efficiency. Many of these technologies were introduced soon after the widespread adoption of filters in the 1960s.

It is known that tobacco smoke microparticulate solids (e.g., total particulate matter; TPM) expresses a high level of fluorescence (20). The fluorescence has been attributed to cyclic compounds in tobacco smoke, particularly those that are classified as polycyclic aromatic hydrocarbons (20). In 1960, McConnell and co-workers at the Tennessee Eastman Company, a major commercial source of cigarette filter fibers ("tow"), reported using the fluorescence of TPM as a means of evaluating cigarette filter efficiency. In the investigation reported by McConnell *et al.* (20), they used five different non-filtered cigarettes. Included also were six different cellulose acetate filters that were capable of removing 20 to 55% of TPM in the tobacco smoke. In the initial experiments, the investigators demonstrated that there was a linear relationship between fluorometric reading and smoke solids from the smoke condensate. With this information at hand, they were able to measure the smoke solids passing through the cigarette filter (indirect method) and the smoke solids collected on the filter (direct method). The results of the fluorometric method compared favorably with the gravimetric (sample weight) method.

Following the studies reported by McConnell (20) and co-workers, Charles Thomas, an investigator at Philip Morris, used the same concept to craft an automated fluorescence-based method for measuring tar of low-delivery cigarettes. The approach used was one in which the TPM was collected from glass-fiber Cambridge filter pads of smoking machines. The Cambridge filters are used in smoking machines to collect TPM to evaluate the vast array of chemicals in cigarette smoke (29). The results of the studies by Thomas (29) confirmed and extended the findings reported by McConnell and co-workers (20) who had shown that there was a linear relationship between filter fluorescence (Ex 365 nm; Em 400 to 600 nm) and the Federal Trade Commission (FTC) "tar" values.

In 1980, Sloan and Curran reported a new method for the spectrophotometric determination of filtration efficiency of cigarette filters (30). The filtration efficiency was determined by dividing the absorbance, measured at 310 nm, of the cigarette filter extract by the combined absorbance of the cigarette filter and Cambridge filter. Once again, an independent group of investigators confirmed and extended prior observations that there was a good correlation between the spectrophotometric methods and the gravimetric method.

Paszkiwicz and Pauly (86) have devised a scheme for measuring TPM on cigarette filters using a procedure in which the filters from smoked Marlboro, Marlboro Ultralight, and 2R4F Reference Standard Cigarettes were dissolved rapidly with 10 ml of anhydrous dimethylsulfoxide (DMSO), manual inversion, then three hours of shaking. Contaminants such as titanium dioxide were removed by centrifuging for 5 minutes. Finally, 0.1 ml of the solution was combined with 1.9 ml of diluent (DMSO:MeOH at 1:2, v/v) for analysis. Scanning spectrofluorometry was conducted with an excitation wavelength (E_x) of 475 nm, and the emission (E_m) wavelength was read at 535 nm. The fluorescent dye acridine orange was used as a surrogate standard. The assay showed a relative standard deviation (RSD) of < 10%. Good linearity (>99%) was observed between machine measured tar and relative fluorescence of extracted filters. The advantage of this and other fluorescence-based procedures is that they provided a technically simple, inexpensive and high-throughput assay suitable for large-scale studies. Also, dissolving the filter circumvented problems associated with the incomplete removal of TPM from Cambridge filters that had been observed when using various solvents (e.g., alcohols) in different extraction procedures.

Considerations for the efficiency of carbon filters—The methods discussed up to this point have focused on efficiency for trapping particulate matter; however, filters can be modified to remove different toxicants and chemicals in tobacco smoke. Filter composition and design is known to effect mouth-level delivery. For example, considerable effort has been made to define the effect of filtration by activated charcoal on the toxicological activity of

cigarette mainstream smoke, particularly the gas-phase components, from conventional and experimental cigarettes.^a The incorporation of activated charcoal into the filter is discussed herein as but one example of filter modification. It is to be noted that despite the extensive interest in charcoal filters, to date, filter-based assays to estimate human exposures from carbon filters have not been developed.

Activated carbon in the filter acts as an adsorbent of the gas phase elements because of its high specific surface area >1000 m²/g. Activated charcoal has an internal structure composed of irregular cavities or pockets, which can be seen readily with a scanning electron microscope. It is effective in removing smoke compounds with boiling points above approximately 30° C. Charcoal is marketed with a range of performance activity (e.g. chemical retention activity). It is characterized further by surface area, pore volume, hardness, density, ash content, pH value and particle size. The performance of the activated carbon is measured by the amount of certain test chemicals the product can absorb. In general, the higher the charcoal activity, the greater the propensity for the filter to retain vapor-phase constituents. For activated carbon used for filtering air and gases, the test chemical used is carbon tetrachloride (CTC). The activated carbon efficiency is expressed as % CTC. Carbon used in cigarette filters may have CTC that range from 50–100%. Methods for assessing the utility of filters with carbon for removing volatile components has also been described Coggins (93), Laugesen (94), Mola (95), Polzin (96), Sarkar (97), Xue (98), Gaworski (footnote “a”) and by investigators at the British American Tobacco Company (99–100).

Different designs have been used in distributing the carbon in the filters, and detailed schemes have been presented in US Patents. Two designs are used frequently. One is the carbon-on-tow design in which the carbon granules are distributed relatively evenly in the cellulose acetate filter plug. This design has been referred to as the “Dalmatian” filter (96). The second design is one in which the charcoal is placed in a cavity of the cellulose acetate filter. In most instances, the cavity is positioned between two plugs to give a plug-space-plug configuration in which the space component is filled with charcoal. Views of these different designs have been presented recently (96).

Studies reported by Polzin *et al.* (96) have compared the mainstream smoke constituent deliveries of cigarettes having different filter designs that had been smoked using three different regimens (ISO, Massachusetts and Health Canada). No significant difference was observed for “tar” and nicotine in comparative studies of same length filters of cellulose acetate without carbon granules and with carbon granules (45 mg). For the same filters and for the same smoking schemes, significant lower deliveries were recorded for the charcoal-containing filter for acetaldehyde, acrolein, benzene, styrene and for the sum of 22 volatile organic compounds. These studies document that charcoal is effective in removing volatile organic compounds from machine-generated mainstream smoke. Overall, the brands with the most charcoal were effective in reducing the volatile organic compounds under even intense smoking conditions (96). There appears a growing body of evidence that cigarettes with activated carbon are effective in reducing certain volatile components in mainstream cigarette smoke as measured with smoking machines, however, there is inadequate information to conclude that the observed reduction will be associated with a reduction in the known risk of diverse smoke-associated maladies, including cancer, pulmonary, and cardiovascular diseases.

In recent studies reported by Philip Morris activated charcoal filtration reduced vapor phase irritants which correlated with a marked decrease in *in vitro* cytotoxicity and *in vivo* morphology of the nose and lower respiratory tract in rat inhalation studies (footnote “a”).

^aGaworski CL, Schramke H, Diekmann J, et al. Effect of filtration by activated charcoal on the toxicological activity of mainstream smoke from experimental cigarettes. *Inhalation Toxicology* 2009; 21:688-704 (ahead of print).

Assays examining deposition of specific chemicals

The desire to determine with greater accuracy smokers' exposures to various toxicants is coupled to a need to account for individual variations in smoking patterns. No two smokers puff identically, although each individual's patterns may be relatively consistent (90,⁹¹). A commercial apparatus for measuring smoke flow has proven useful for measure puffing behavior (e.g., CReSS Lab Products; Borgwaldt KC GmbH) and the reliability of these devices has been studied (15,⁸⁹). However, these and related flow meters require the use of mouthpieces that may interfere with normal smoking behavior, and require that the smoker use the device. Assaying the spent cigarette filter provides a proxy that bypasses the need for a mouthpiece or mechanical flow meter. Chemically-specific assays can be used to correlate levels of one chemical to yields of toxicants to estimate yield in use. Two approaches have been put forward, each of which is discussed in detail below.

Assessing nicotine in the filter—A logical measure of mouth-level exposure would be nicotine trapped in the filter. Indeed, CORESTA issued a recommended spectrophotometric method for testing this in 1968 (101) and scientists at PM used such assays for in-house studies of smoking behavior in the early 1970s (102–104). Industry scientists developed a liquid chromatography approach in the 1980s. A liquid chromatography procedure was described in 1985 for the analysis of nicotine on cellulose acetate filters by Green and colleagues of the R. J. Reynolds Tobacco Company (37). In this method, the cellulose acetate filter was dissolved in acetonitrile to release any trapped nicotine. The investigators showed that the nicotine was stable on the filter, and that the proposed method was successful in circumventing problems previously encountered in removing nicotine from aged cigarette filters.

The measurement of nicotine on filters has recently been reintroduced by Shepperd and co-workers (73) at the British American Tobacco Company who have described the validation of methods for determining consumer smoked cigarette yields from cigarette filter analysis. Two methods have been detailed. The first method, a whole filter scheme, is based on the analysis of whole filters using average values of filtration efficiencies obtained from a range of machine smoke puffing regimens. Procedurally, the filters are split longitudinally, cut in half transversally and then solvent extracted. The nicotine content of the extract was then determined by gas chromatography with flame ionization detection as per CORESTA Recommended Method No.9 (105). The second method is a part filter scheme that analyzes a 10-mm section from the mouth end of the filter, where the filtration efficiency remains relatively constant irrespective of puff flow rates and butt lengths. The analysis methods were largely equivalent with the exception of the extraction solution. Here also extract 'tar' content was estimated with a ultraviolet (UV) light absorbance using capillary electrophoresis and UV detection. Relative standard deviation (RSD) averaged 5%, and no information regarding recovery or limit of detection (LOD) was provided. The investigators reported that both filter methods gave good correlations with nicotine and tar yields. However, the part filter method was reported to be less susceptible to the effect of nicotine condensation and gave a more accurate assessment of yields than the whole filter method. The findings showed that the filter can be used for measuring tar and nicotine yields from cigarettes by smokers in their normal smoking environments. In addition, the methodology may provide a better understanding of the relationship between yields recorded for smokers versus different machine smoking regimens such as the ISO and Federal Trade Commission (FTC) protocol developed in 1967.

The same group of investigators at British American Tobacco Company also has reported a comparison in smokers of cigarette filter nicotine levels, salivary cotinine and urinary excretion of nicotine and its metabolites (72). The primary objective of this investigation was to determine the suitability of these different methodologies for estimating nicotine exposure and absorption in smokers. The research scheme was a five day clinical study of 74 smokers who

smoked their own brands *ad libitum*. Filters were assessed as in the earlier Shepperd publication (73). The results showed that each method showed a high correlation ($p < 0.01$) with the other two methods. The best correlation, however, was obtained between the filter nicotine analysis and urinary nicotine and nicotine metabolites. The pooled coefficient of variation (CV) within-subjects across the study was 17.8%, consistent with the CV for saliva cotinine, urinary nicotine, nicotine metabolites and reported cigarette use. The authors concluded that the filter analysis was less complicated and intrusive, and that the filters can be collected easily and without supervision. The authors note also that biomarker measurement in blood/plasma and smoking behavior measurements require that sampling or measurements must be performed in a laboratory environment.

Recent data assessing filters and biospecimens collected from German smokers in an ambulatory study (139) confirmed the earlier findings with respect to nicotine exposure and further compared filter nicotine to urinary biomarkers, including tobacco-specific N-nitrosamine, 1-hydroxy pyrene, and acrolein. This study showed that estimates of exposure obtained by filter analysis and biomarkers of exposure correlated significantly over a wide range of smoke exposures and that filter analysis may provide a simple and effective alternative to biomarkers for estimating smokers' exposure.

Assessing solanesol in the filter—Another chemical that can be measured in the filter to act as a proxy to exposure is solanesol. Solanesol is a tobacco-specific compound that is found in leaf tobacco and commercial tobacco products (55). It is a nonvolatile trisesquiterpenoid alcohol and withstands degradation during the burning of cigarettes (104–106). Solanesol has been used to measure the deposition and retention of cigarette smoke, and different components therein, in the lung (reviewed in 109). While UV light and ozone have been shown to degrade solanesol (110), Tucker and Pretty reported that solanesol within the cigarette filter is not extensively exposed to sunlight or ozone, so this issue does not affect a filter assay result. An initial investigation in 2005 reported initial steps to assess levels of solanesol in the whole cigarette filter (110). In brief, the procedure requires the removal of the outer tipping paper from the filter and separating the filter fibers manually to expose more surface area. The filters are then solvent extracted and the extract is analyzed by high performance liquid chromatography (HPLC) and tandem mass spectrometry (MS/MS) with atmospheric pressure chemical ionization. The authors report recovery of 99.85% and relative standard deviation of 5.35%. The LOD was 1.5 ng of solanesol on the column. Experiments by the authors showed that loss of solanesol from filters due to storage at room temperature was minimal (approximately 0.4% per day). Filters of cigarettes smoked on smoking machines under ISO conditions were assessed for filter solanesol levels (110). Marlboro Light[®] cigarettes were smoked in triplicate with the total puff count increasing from 1 to 7. The assay showed good linearity for puff number and puff volume. Filter solanesol also was highly correlated with tar and nicotine yields. Finally, the authors also assessed vent hole blocking and the good linearity was maintained for tar and nicotine. The authors concluded that filter solanesol meets criteria for a good smoke marker, providing a noninvasive means for assessing mouth-level some exposure for individuals.

A recent paper (88) extended and modified the original filter solanesol method. First, rather than using the whole filter, the final 10 mm nearest the mouth end only was used, consistent with the work by Shepperd and colleagues (110), discussed above. Polzin and colleagues (88) explored the use of a high throughput and low solvent method, wherein filters were added to high volume 48-well plates and loaded into an automated workstation that adds solvent. This was then followed by transfer to 96-well plates for LC/MS analysis. A surrogate internal standard, geranylgeraniol, which is structurally similar to solanesol, is added. Using this method, the amount of solanesol retained in the filter was determined to be a function of the mainstream smoke delivery of both nicotine and tar. The authors reported recovery of 96%

and relative SD of 10% under the prior preparation, compared to 95% and 11% for the low solvent method, making them comparable. To test the utility of the methods, the authors generated butts from Kentucky Reference cigarettes (2R4F) under ISO and Canadian Intense smoking conditions, with variations in puff number from 2 to the full tobacco rod length. Excellent linearity was recorded for both the standard solvent and low solvent. The authors concluded that the modified method offered substantial savings at negligible change to outputs. The authors report that the new preparation and analysis methods increased throughput fivefold relative to the prior method, meaning the ability to examine up to 250 samples per day on a single mass spectrophotometer. Thus, the measurement of solanesol provides a noninvasive and sensitive measure of tobacco smoke exposure. Further, solanesol in cigarette butts is stable; thus, the filters can be collected, stored and processed as a batch when convenient. Studies assessing filter solanesol to human exposure and biomarkers have not yet been done.

Summary of Findings

Table 3 tabulates a brief summary of the advantages and disadvantages of the different identified cigarette filter-based assays. Research gaps and opportunities to utilize cigarette-filter based assays as a means to assess individual variation in exposure to tobacco smoke constituents are presented in Table 4. The ultimate question is whether the filter-based assays have utility as proxy measures. Validation attempts for the methods have focused on correlation with specific smoke emissions and/or biomarkers of exposure in humans.

Correlation of filter-based assays with specific smoke emissions

Polzin and colleagues (88) validated their standard and modified methods for solanesol measurement against NNN and NNK emissions. They reported that, indeed, filter solanesol can be used to estimate machine delivery of both carcinogens, with good linearity ($R^2=0.9673$ for NNN and 0.9512 for NNK). The estimated deliveries of both constituents (based on solanesol) were consistent with prior reports of deliveries in the literature. Shepperd and colleagues (139) did not report the correlation between filter nicotine and emissions of acrolein, NNK, or pyrene *per se*. Rickert demonstrated that tar color components could model 10 smoke constituent yields generated across a range of smoking conditions, with relative standard deviations that ranged from 8.1% (1,3-butadiene) to 51.4% (NNK).

Correlation of filter-based assays with biomarkers

Biomarkers of exposure are an important consideration in the evaluation of PREPs, tobacco products and, more broadly, disease prevention (111,¹¹²). Filters can impact the chemical composition and toxicity of cigarette mainstream smoke (reviewed in 113–116). So, demonstrating a relationship between filter-based assays and biomarkers of exposure would add strength to its utility as a proxy measure of mouth level exposure. Existing data thus far indicate that the part-filter nicotine assays show significant relationships to nicotine intake, and at least the part-filter method has data linking it to NNAL, HPMA, and 1-OHP levels in smokers. However, data on eluted tar and visual inspection/imaging are lacking in this area. O'Connor and colleagues (80) for example showed a low correlation between salivary cotinine and staining intensity.

Discussion

The results of this structured review have shown that: (a) sufficient data exists to link filter-based chemical measures to ISO yields of tar and nicotine; (b) tar eluted from filters or in chemical digest of filters can be used to estimate the efficiency of the filter for trapping smoke solids; (c) visual and/or digital inspection of filters can be used as indicators of smoking behaviors such as filter vent blocking, number of puffs taken, and total volume drawn; (d)

limited data suggest a correlation between solanesol and nicotine measured in filters and exposure biomarkers in smokers.

Research Gaps and Future Directions

Linkage of filter-based assays to biomarkers of exposure other than nicotine and with biomarkers of biological effect is needed to truly test whether filter-based assays can serve as proxy measures of mouth-level exposure. It is important to clarify that a filter-based assay cannot in itself be a measure of exposure; smokers are exposed to what is NOT trapped by the filter. That is, smokers are exposed to what passes through the filter, and conversely are unexposed to what was captured by the filter. There is a limit to the relationship between such a measure and a biomarker, which is a product of factors inherent to the individual (e.g., gender, age, metabolism, and genetic makeup).

There is a noticeable absence of head-to-head comparison of the different assays. That is, individual laboratories and research groups have developed and favor specific assays. In principle, the methods should have some overlap. Future studies, however, should characterize inter-correlations among different filter-based assays where do they overlap, and where do some outperform others? For widespread applicability, a multi-laboratory validation process would be preferable to determine the inter-assay reliability of the various methods.

All the research we identified using filter based assays has relied exclusively on conventional cellulose acetate filters. However, a major consideration not specifically addressed is the role of filter design characteristics (e.g., density, fiber denier, length, and overall efficiency) may play in the interpretation of assay results. At a minimum, some measurement of the unsmoked filter would need to be considered as a potential covariate or adjustment factor. Also, no published studies which have incorporated PREPs and other smoking articles (i.e., electrically heated cigarettes) that are being promoted as reduced-risk products. Likewise, the majority of studies did not document the application of the technology for assessing cigarettes with filters containing charcoal, ion resins, embedded flavor elements or other agents that have been incorporated into the filter. Thus, further research is required to assure that a proposed assay is applicable across different filter designs, or to define those filter designs for which particular assays may be unsuited.

Some of the proposed assays are technically complex in that they require multiple-step processing of the sample or expensive analytical instrumentation, such as the measurement of chemical deposition on filters for nicotine or solanesol. Such assays might prove challenging to translate to laboratories in developing countries, and such assays may not be applicable for large-scale screening studies. High-throughput and inexpensive technologies that can be applied to both conventional and modified reduced risk cigarettes are needed, and additional investigations, particularly those that incorporate biomarkers of exposure, are required.

Many of the reported studies did not systematically address issues relating to storage and stability of the filters, and problems that may arise in stored filters from previously conducted studies. This is a particular concern for an assay whose best utility might be in field studies where tight controls on sample storage and handling may be impossible. Watson and colleagues noted the semi volatility of nicotine as a reason that they chose solanesol as their marker (55, 57). Solanesol loss from filters stored at room temperature was estimated at 0.4% per day. Similar data on the loss rate for nicotine would be desirable, as would data on stability under different storage conditions, such as room temperature, refrigerated (4° C), frozen (−20° C), and ultralow freezing (−70° C). Similarly, the impact of storage conditions and time from smoking on visual inspection and image-based assays could be better characterized.

In conclusion, emerging literature suggests that assays making use of the cigarette filter may prove useful in estimating smoking behaviors such as topography and filter vent blocking, and may have utility as proxy measures of mouth-level smoke exposure. The limited studies to date have not compared the methods directly, so it cannot yet be said whether one approach is superior or inferior to others. However, it may be possible to use filters as surrogates or estimators of exposure, depending on the sensitivity of the assay, correlations with established measures of exposure in smokers, product characteristics and the specific research question(s) being posed.

Acknowledgments

The cost of this literature review was supported by National Cancer Institute contract HHSN261200644002 (Laboratory Assessment of Tobacco Use Behavior and Exposure to Toxins Among Users of New Tobacco Products Promoted to Reduce Harm)

Abbreviations

Authors' note: The tabulation of abbreviations is not a format used in Cancer Epidemiology Biomarkers & Prevention, but has been included to facilitate reviewing of the manuscript).

CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CTC	carbon tetrachloride
CV	coefficient of variation
ISO	International Organization for Standardization
LC/MS	combination of liquid chromatography and mass spectrophotometry
LOD	limit of detection
NNAL	tobacco specific 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	tobacco-specific 4-(methylnitrosamino)- 1-(3-pyridyl)-1-butanone
NNN	tobacco specific N-Nitrosornicotine
PREPs	potential reduced exposure products
RSD and SD	relative standard deviation
TPM	total particulate matter

References

Authors' note: A [LINK] has been provided to enable the reviewers to access the paper; the [LINK] can be activated by striking simultaneously <Ctrl and left-hand mouse button click>. All literature cited herein will be made available to all interested parties via an open forum, such as that which is provided by the "Tobacco Documents" site of the Roswell Park Cancer Institute.

1. Stratton, K.; Shetty, P.; Wallace, R.; Bondurant, S. Clearing the smoke: The science base for tobacco harm reduction. Washington, D.C: National Academy Press, Institute of Medicine, Washington DC; 2001. p. 636
2. False and Misleading advertising (filter-tip cigarettes) hearings before a subcommittee of the committee on government operations. House of Representatives, 85th Congress, first session; 18 July 1957; p. 799
3. Federal Trade Commission. Cigarette report for 2004 and 2005. Washington DC: Federal Trade Commission; 2007.

4. Fairchild A, Colgrove J. Out of the Ashes: The life, death and rebirth of the “safer” cigarette in the United States. *Am J Public Health* 2004;94:192–204. [PubMed: 14759927]
5. Rees VW, Wayne GF, Thomas BF, Connolly GN. Physical design analysis and mainstream smoke constituent yields of the new potential reduced exposure product, Marlboro *UltraSmooth*. *Nicotine Tob Res* 2007;9:1197–1206. [PubMed: 17978995]
6. Norman, A. Cigarette design and materials. In: Davis, DL.; Nielsen, MT., editors. *Tobacco – Production, Chemistry and Technology*. Vol. Chapter 11B. Blackwell Science Ltd; Oxford: 1999. p. 353–387.
7. Hatsukami DK, Giovino GA, Eissenberg T, Clark PI, Lawrence D, Leischow S. Methods to assess potential reduced exposure products. *Nicotine Tob Res* 2005;7:827–44. [PubMed: 16298718]
8. Hatsukami DK, Benowitz NL, Rennard SI, Oncken C, Hecht SS. Biomarkers to assess the utility of potential reduced exposure tobacco products. *Nicotine Tob Res* 2006;8:169–91. [PubMed: 16766411]
9. National Cancer Institute. *Smoking and Tobacco Control Monograph 13*. Bethesda: NCI; 2001. Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine.
10. Hecht SS, Murphy SE, Carmella SG, et al. Similar uptake of lung carcinogens by smokers of regular, light, and ultralight cigarettes. *Cancer Epidemiol Biomarkers Prev* 2005;14:693–8. [PubMed: 15767351]
11. Bernert JT, Jain RB, Pirkle JL, Wang L, Miller BB, Sampson EJ. Urinary tobacco-specific nitrosamines and 4-aminobiphenyl hemoglobin adducts measured in smokers of either regular or light cigarettes. *Nicotine Tob Res* 2005;7:729–38. [PubMed: 16191744]
12. Benowitz NL, Jacob P III, Bernert JT, et al. Carcinogen exposure during short-term switching from regular to “light” cigarettes. *Cancer Epidemiol Biomarkers Prev* 2005;14:1376–83. [PubMed: 15941944]
13. Scherer G, Engl J, Urban M, Gilch G, Janket D, Riedel K. Relationship between machine-derived smoke yields and biomarkers in cigarette smokers in Germany. *Regul Toxicol Pharmacol* 2007;47:171–83. [PubMed: 17034917]
14. Burns DM, Dybing E, Gray N, et al. Mandated lowering of toxicants in cigarette smoke: a description of the World Health Organization. *TobReg proposal*. *Tob Control* 2008;17(2):132–41. [PubMed: 18375736]
15. Hammond D, Fong GT, Cummings KM, O’Connor RJ, Giovino GA, McNeill A. Cigarettes yields and human exposure: a comparison of alternative testing regimens. *Cancer Epidemiol Biomarkers Prev* 2006;15:1495–501. [PubMed: 16896039]
16. Andersson G, Vala EK, Curvall M. The influence of cigarette consumption and smoking machine yields of tar and nicotine on the nicotine uptake and oral mucosal lesions in smokers. *J Oral Pathol Med* 1997;26:117–123. [PubMed: 9083935]
17. Webb, EJ.; Campbell, DT.; Schwartz, RD.; Sechrest, L. *Unobtrusive measures: Nonreactive Research in the Social Sciences*. Chicago: Rand McNally; 1966.
18. Mellors RC, Hlinka J, Stoholski A. In vivo cellular localization of fluorescent materials derived from cigarette smoke. *Amer Assoc Cancer Res*. 1957 Abstract.
19. Bentley HR, Burgan JG. Polynuclear hydrocarbons in tobacco and tobacco smoke. *Analyst* 1958;83:442–47.
20. McConnell WV, Mumpower RC II, Touey GP. Evaluation of cigarette filter efficiency by photofluorometry. *Tob Sci* 1960;4:56–61.
21. Service d’Exploitation Industrielle des Tabacs et des Allumettes (SEITA). Comparative investigation on the measurement of filter efficiency results of an international collaborative investigation carried out by the Coresta Smoke Technology group. *Beitr Tabakforsch Int* 1963;21:1–35.
22. Vilcins G, Varsel CJ, Resnik FE. Infrared method for evaluation of cigarette filter efficiency [Abstract]. *Tob Sci* 1964;8:49–52.
23. Lipp G. The selective effect of cigarette filters on the nicotine and phenol retention in different tobacco types. *Beitr Tabakforsch Int* 1965;3(2):109–127. [Article in German].
24. CORESTA. Determination of Alkaloid Retention by Cigarette Filters. Recommended Method No. 13. September;1968
25. Pillsbury HC, Bright CC, O’Connor KJ, Irish FW. Tar and nicotine in cigarette smoke. *J Assoc Offic Anal Chem* 1969;52:458–62.

26. Curran JG, Kiefer JE. A method for measuring the elution of nicotine and total particulate matter from a cigarette filter. *Beitr Tabakforsch Int* 1973;7:29–35.
27. Forbes WF, Robinson JC, Hanley JA, Colburn NH. Studies on the nicotine exposure of individual smokers changes in mouth-level exposure to nicotine on switching to lower nicotine cigarettes. *Int J Addict* 1976;11:933–50. [PubMed: 1030688]
28. Burton, FG.; Veal, JT.; Phelps, DW. Quantitative analysis of cigarette tars using fluorescent spectroscopy [paper #51]. American Chemical Society Spring National Meeting; 1977 Mar 20–25; New Orleans, LA.
29. Thomas CE. Automated method for FTC tar of low delivery cigarettes based upon fluorescence of TPM extracts. *Tob Sci* 1980;24:64–8.
30. Sloan CH, Curran JG. Spectrophotometric determination of filtration efficiency of cigarette filters. *Tob Sci* 1980;26:57–60.
31. Robinson JC, Young JC. Temporal patterns in smoking rate and mouth-level nicotine exposure. *Addict Behav* 1980;5:91–5. [PubMed: 7405663]
32. Kozlowski LT, Frecker RC, Khouw V, Pope MA. The misuse of ‘less-hazardous’ cigarettes and its detection: hole-blocking of ventilated filters. *Am J Public Health* 1980;70:1202–3. [PubMed: 7425194]
33. Kozlowski LT, Rickert WS, Pope MA, Robinson JC. A color-matching technique for monitoring tar/nicotine yields to smokers. *Am J Public Health* 1982;72:597–9. [PubMed: 7072878]
34. Lombardo T, Davis CJ, Prue DM. When low tar cigarettes yield high tar: cigarette filter ventilation hole blocking and its detection. *Addict Behav* 1983;8:67–9. [PubMed: 6880926]
35. Norman V, Ihrig AM, Shoffner RA, Ireland MS. The effect of tip dilution on the filtration efficiency of upstream and downstream segments of cigarette filters. *Beitr Tabakforsch Int* 1984;12(4):178–85.
36. Devitt G, West RJ, Jarvis M. Test for assessing tar/nicotine yields [letter to the editor]. *Am J Public Health* 1984;74:391. [PubMed: 6703172]
37. Green CR, Conrad FW, Bridle JKA, Borgerding MF. A liquid chromatography procedure for analysis of nicotine on cellulose acetate filters. *Beitr Tabakforsch Int* 1985;13(1):11–6.
38. Zacny JP, Stitzer ML, Yingling JE. Cigarette filter vent blocking: effects on smoking topography and carbon monoxide exposure. *Pharmacol Biochem Behav* 1986;25:1245–52. [PubMed: 3809227]
39. Kozlowski LT, Pope MA, Lux JE. Prevalence of the misuse of ultra-low-tar cigarettes by blocking filter vents. *Am J Public Health* 1988;78:694–5. [PubMed: 3369602]
40. CORESTA. Recommended Method No. 9, Determination of Nicotine in Cigarette Filters by Gas Chromatographic Analysis. October;1989
41. Kozlowski LT, Pillitteri JL, Sweeney CT. Misuse of “light” cigarettes by means of vent blocking. *J Subst Abuse* 1994;6:333–6. [PubMed: 7703710]
42. Pillitteri JL, Morse AC, Kozlowski LT. Detection of vent-blocking on light and ultralight cigarettes. *Pharmacol Biochem Behav* 1994;48:539–42. [PubMed: 8090828]
43. Rickert, WS.; Robinson, JC.; Kaiserman, MJ. Quantitation of “tar” colour with specific reference to estimating yields, quantifying ETS and the production of colour scales. 48th Tobacco Chemists’ Research Conference; 1994; Greensboro, NC.
44. Kozlowski LT, Sweeney CT, Pillitteri JL. Blocking cigarette filter vents with lips more than doubles carbon monoxide intake from ultra-low tar cigarettes. *Exp Clin Psychopharmacol* 1996;4:404–8.
45. Porter A, Dunn P. Mouth insertion depths in Canadian smokers. *Beitr Tabakforsch Int* 1998;18:85–91.
46. Sweeney, CT. Experimental research on the behavioral blocking of filter vents on low- yield cigarettes [dissertation]. Pennsylvania State University; 1998.
47. Baker RR, Dixon M, Hill CA. The incidence and consequences of filter vent blocking among British smokers. *Beitr Tabakforsch Int* 1998;18:71–83.
48. Determination of filter efficiency in mainstream tobacco smoke. Health Canada. 1999
49. Pauly, JL. The third phase of mainstream cigarette smoke identified as fibers and particles released from cigarette filters [abstract and slides]. 11th World Conference on Tobacco; 2000 Apr 6–11; Chicago, IL.

50. Husset M, Chaouat V, Lethu T, Victoria R. Ne premiere: le nuancier guodrons. [Premier: shades of tar]. 60 Millions de Consommateurs 2000;358:36–40. [Article in French].
51. Baker RR, Lewis LS. A review of the incidence and consequences of cigarette filter vent blocking among smokers. Beitr Tabakforsch Int 2001;19:209–28.
52. Lesser, CA.; Von Borstel, RW. Tobacco Smoke Filter. Assigned to Filligent Limited, Central (Hong Kong Special Administrative Reg). PCT Pub. United States patent 6,792,953. 2002 Mar 21. p. B2
53. St Charles, FK.; Kabbani, AA.; Cowart, ML. Estimation of consumer-smoked cigarette yields for a wide range of cigarette designs. 56th Tobacco Research Conference, Program Booklet and Abstracts; Paper 28, 2002; p. 35 and color prints of a slide presentation. See also footnote.^b
54. Hu Q, Liu Z, Ma J, Peng L, Bai H. Cigarette mouth insertion depths among Chinese smokers. Beitr Tabakforsch Int 2003;20(7):476–80.
55. Watson C, McCraw J, Polzin G, Ashley D. Development of a method to assess cigarette smoke intake. Environ Sci Technol 2004;38:248–53. [PubMed: 14740743]
56. Rickert, WS.; Wright, WG.; Kaiserman, MJ. Measured cigarette filter colour (CIELab) after smoking as a predictor of mouth level exposure to selected Hoffmann analytes [slide presentation]. CORESTA Paper No. SS 5; 2004 CORESTA congress; 2004 Oct 3–7; Kyoto, Japan.
57. Calafat AM, Polzin GM, Saylor J, Richter P, Ashley DL, Watson CH. Determination of tar, nicotine and carbon monoxide yields in the mainstream smoke of selected international cigarettes. Tob Control 2004;13:45–51. [PubMed: 14985595]
58. Strasser AA, Ashare RL, Kozlowski LT, Pickworth WB. The effect of filter vent blocking and smoking topography on carbon monoxide levels in smokers. Pharmacol Biochem Behav 2005;82:320–9. [PubMed: 16213579]
59. St. Charles, K.; Krautter, G.; Mariner, D. A comparison of human nicotine dose estimates from filter analysis with nicotine metabolites analysis [poster POS1–005]. 11th Annual Meeting and 7th Annual European Conference of the Society for Research on Nicotine and Tobacco; 2005 Mar 20–23; Prague, Czech Republic.
60. PM USA Brand Styles and Non-PM USA Brand Styles. Massachusetts Department of Public Health Meeting; Boston. Feb. 7, 2005; Slide: (Benzo[a]pyrene Yields with Massachusetts Tar Yields (Machine Smoking)PM USA -- Slide #21
61. Prignot JJ, Jamart J. What can be learnt from tobacco butts? An observational study in a realistic hospital setting. Int J Tuberc Lung Dis 2005;9:210–5. [PubMed: 15732743]
62. Pickworth W, Houlgate P, Schorp M, Dixon M, Borgerding M, Zaatari G. A review of human smoking behaviour data and recommendations for a new ISO standard for the machine smoking of cigarettes. A Report of the Ad Hoc WG9 Smoking behaviour Review Team to ISO/TC 126 WG 9. August 10;2005
63. O'Connor RJ, Stitt JP, Kozlowski LT. A digital image analysis system for identifying filter vent blocking on ultralight cigarettes. Cancer Epidemiol Biomarkers Prev 2005;14:533–7. [PubMed: 15734984]
64. Mariner, DC.; McEwan, M.; St Charles, FK.; Krautter, G.; Appleton, S. Dose-response relationships for urinary biomarkers of selected tobacco smoke constituents [poster POS1–001]. 11th Annual Meeting and 7th Annual European Conference of the Society for Research on Nicotine and Tobacco; 2005 Mar 20–23; Prague, Czech Republic.
65. Kozlowski, LT. Puff Topography What is it good for?. Slide presentation at the Biological and Environmental Measurement in Tobacco Research: A Transdisciplinary Workshop; CAMH, Toronto, Canada. May 19–20, 2005; Power Point Slide Presentation
66. Hammond D, Fong GT, Cummings KM, Hyland A. Smoking topography, brand switching and nicotine delivery: Results from an in vivo study. Cancer Epidemiol Biomarkers Prev 2005;14:1370–5. [PubMed: 15941943]
67. Estimation of human smoke nicotine and NFDPM yield by analysis of subjects' part filters post smoking. DRAFT. E-mail to Dr. Pauly from Mike_Dixon@bat.com. Subject: Filter analysis details.

^bAccepted manuscript, released ahead of publication: “Estimating tar and nicotine exposure: Human smoking versus machine generated smoke yields,” St. Charles FK, Kabbani AA, Borgerding MF. Regulatory Toxicology and Pharmacology. [LINK] *Authors' note:* This manuscript has recently been accepted. Reference to this paper and additional information regarding the publication date will be added.

- May 19, 2005 Attached Word document: Draft Part Filter Method.doc (241 MB) and PDF file 28-St. Charles, F.K. PDF (480 MB). Presented at 2005 SRNT meeting in Prague.
68. Dixon, M.; Shepperd, J.; St Charles, K. Validation of cigarette filter analysis methods for estimating tar and nicotine yields to smokers [poster POS1-008]. 11th Annual Meeting and 7th Annual European Conference of the Society for Research on Nicotine and Tobacco; 2005 Mar 20-23; Prague, Czech Republic.
 69. Tar, Nicotine and Carbon Monoxide values for most market cigarette brands. Tobacco Industry Testing Laboratory, Market Sample #47. Kindly provided to Dr. Pauly by Dr. Richard O'Connor, e-mail communication of 01-09-06. Information obtained by Dr. O'Connor via Freedom of Information Act (FOIA).
 70. Tar, Nicotine and Carbon Monoxide values for most market cigarette brands. Tobacco Industry Testing Laboratory. Market Sample #46. Kindly provided to Dr. Pauly by Dr. Richard O'Connor. E-mail communication of 01-09-06. Information obtained by Dr. O'Connor via FOIA.
 71. Strasser AA, O'Connor RJ, Mooney ME, Wileyto EP. Digital image analysis of cigarette filter stains as an indicator of compensatory smoking. *Cancer Epidemiol Biomarkers Prev* 2006;15:2565-9. [PubMed: 17164388]
 72. St Charles FK, Krautter GR, Dixon M, Mariner DC. A comparison of nicotine dose estimates in smokers between filter analysis, salivary cotinine, and urinary excretion of nicotine metabolites. *Psychopharmacology* 2006;189:345-54. [PubMed: 17028908]
 73. Shepperd CJ, St Charles FK, Lien M, Dixon M. Validation of methods for determining consumer smoked cigarette yields from cigarette filter analysis. *Cont Tob Res* 2006;22:176-84.
 74. Rennard. Lung Disease Caused by Cigarette Smoke. University of Nebraska. Slide Presentation. NCI Workshop. Feb 1, 2006 TTURC Grant Power Point Slides.
 75. Ou B, Huang D. Fluorescent approach to quantitation of reactive oxygen species in mainstream cigarette smoke. *Anal Chem* 2006;78:3097-103. [PubMed: 16642999]
 76. Lubin JH, Caporaso NE. Cigarette smoking and lung cancer: Modeling total exposure and intensity. *Cancer Epidemiol Biomarkers Prev* 2006;15:517-23. [PubMed: 16537710]
 77. Cummings KM, Brown A, Douglas CE. Consumer acceptable risk. How cigarette companies have responded to accusations that their products are defective. *Tob Control* 2006;15(Suppl 4):iv84-9. [PubMed: 17130628]
 78. Ashley DL. Analysis of Product, Smoke and Biomarkers in Evaluating the Health Impact of Tobacco Use. Feb 1, 2006. Slide presentation. Grant TTURC Power Point Slides. color copy (12a) and black and white copy (12b).
 79. Shepperd, CJ.; McEwan, M. A study design to investigate the influence of FTC/ISO tar yield and tar brand switching on cigarette smoke dose as determined by filter analysis and biomarkers of exposure [poster RPOS3-115]. 13th Annual Meeting of the Society for Research on Nicotine and Tobacco; 2007 Feb 21-24; Austin, TX.
 80. O'Connor RJ, Kozlowski LT, Hammond D, Vance TT, Stitt JP, Cummings KM. Digital image analysis of cigarette filter staining to estimate smoke exposure. *Nicotine Tob Res* 2007;9:865-71. [PubMed: 17654299]
 81. Strasser, AA.; Sanborn, PM.; Tang, KZ.; Zhou, JY. The effect of filter vent blocking, smoking topography and filter tar stain scoring on carbon monoxide boost [poster POS1-123]. 13th Annual Meeting of the Society for Research on Nicotine and Tobacco; 2007 Feb 21-24; Austin, TX.
 82. Morton, MJ.; Williams, DL.; Hjorth, HB.; Smith, JH. Philip Morris USA Inc. Cigarette filter color as an estimator of cigarette tar yield [poster POS1-124]. 13th Annual Meeting of the Society for Research on Nicotine and Tobacco; 2007 Feb 21-24; Austin, TX.
 83. Mariner, DC.; Booty, M.; Mullard, G.; Shepperd, CJ. A comparison of German smokers' exposure to tar and nicotine using analysis of smoked cigarette filters with yields from a range of machine smoking regimes [poster 34]. 9th Annual European Meeting of the Society for Research on Nicotine and Tobacco; 2007 Oct 3-6; Madrid, Spain.
 84. Shepperd, CJ.; Mariner, DC.; McEwan, M.; O'Reilly, D.; Eldridge, A. A study to estimate and correlate cigarette smoke exposure as determined by filter analysis and biomarkers of exposure. 14th Annual Meeting of the Society for Research on Nicotine and Tobacco; 2008 Feb 27 & 28, Mar 1; Portland, OR.

85. Thomson G, Wilson N, Bushell L, et al. Butt lengths differ by area deprivation level: A field study to explore intensive smoking. *Nicotine Tob Res* 2008;10(5):927–31. [PubMed: 18569769]
86. Paszkiewicz GM, Pauly JL. Spectrofluorometric method for measuring tobacco smoke particulate matter on cigarette filters and Cambridge pads. *Tob Control* 2008;17(Suppl 1):i53–i58. [PubMed: 18768460]
87. Mariner, DC.; Slayford, SJ.; Nother, K.; Shepperd, CJ. A comparison of the plowshare CRESSMICRO smoking topography analyser with a proprietary smoking analyser. 14th Annual Meeting of the Society for Research on Nicotine and Tobacco; 2008 Feb 27 & 28, Mar 1; Portland, OR.
88. Polzin GM, Wu W, et al. Estimating smokers' mouth-level exposure to select mainstream smoke constituents from discarded cigarette filter butts. *Nicotine Tob Res* 2009;11:868–874. [PubMed: 19541951]
89. Blank MD, Disharoon S, Eissenberg T. Comparison of methods for measurement of smoking behavior: mouthpiece-based computerized devices versus direct observation. *Nicotine Tob Res* 2009 Jul;11(7):896–903. [PubMed: 19525207]
90. Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *J Natl Cancer Inst* 2000;92:106–11. [PubMed: 10639511]
91. Melikian AA, Djordjevic MV, Chen S, Richie J Jr, Stellman SD. Effect of delivered dosage of cigarette smoke toxins on the levels of urinary biomarkers of exposure. *Cancer Epidemiol Biomarkers Prev* 2007;16:1408–15. [PubMed: 17627005]
92. Philip, Morris. Dictionary of Tobacco Terminology.
93. Coggins CRE, Gaworski CL. Could charcoal filtration of cigarette smoke reduce smoking-induced disease? A review of the literature. *Regul Toxicol Pharmacol* 2008;50:359–365. [PubMed: 18289753]
94. Laugesen M, Fowles J. Marlboro UltraSmooth: a potentially reduced exposure cigarette? *Tob Control* 2006;15:430–5. [PubMed: 17130370]
95. Mola M, Hallum M, Branton P. The characterisation and evaluation of activated carbon in a cigarette filter. *Adsorption* 2008;14:335–341.
96. Polzin GM, Zhang L, Hearn BA, et al. Effect of charcoal-containing cigarette filters on gas phase volatile organic compounds in mainstream cigarette smoke. *Tob Control* 2008;17(Suppl 1):i10–6. [PubMed: 18768454]
97. Sarkar M, Kapur S, Frost-Pineda K, et al. Evaluation of biomarkers of exposure to selected cigarette smoke constituents in adult smokers switched to carbon-filtered cigarettes in short-term and long-term clinical studies. *Nicotine Tob Res* 2008;10:1761–72. [PubMed: 19023827]
98. Xue L, Thomas CE, Koller KB. Mainstream smoke gas phase filtration performance of adsorption materials evaluated with a puff-by-puff machine GC-MS method. *Beitr Tabakforsch Int* 2002;20:251–6.
99. British American Tobacco Company. Active charcoal as a constituent of cigarette filters. 1965. p. 54TobaccoDocuments.org Bates: 402368992–402369045. Retrieved 09-09-09
100. British American Tobacco Company Limited. R&D-B09–94 Charcoal filter development Evaluation of commercial filter designs. Research & Development. Legacy Tobacco Documents Library; Bates 402382486–402382511. Retrieved 09-09-09
101. Centre for Cooperation for Research Relative to Tobacco (CORESTA). Determination of alkaloid retention by cigarette filters (September 1968). Recommended Method No.12. Confidential.
102. Schori, TR.; Jones, BW. Does the smoker compensate for the changes in delivery in order to regulate intake (TNT-4). Philip Morris USA; Aug. 1974 Bates 2062951144–2062951168. Retrieved 09-09-09
103. Duggins, J.; Dunn, WL.; Schori, T.; Thomson, R. Confidential. Philip Morris USA; Mar. 1973 Smoker psychology smoking behavior: Real world observations. Bates 1000353355–1000353357. Retrieved 09-09-09
104. Ryan, F. Confidential. Philip Morris USA; Jun. 1970 Project 1600 SEX II. Evaluation Report #415 Changes in FTC intake produced by changes in FTC delivery. Bates 1003286591–1003286612. Retrieved 09-09-09

105. Centre for Cooperation for Research Relative to Tobacco (CORESTA). Determination of nicotine in cigarette filters by gas chromatography analysis (April 2009). Recommended Method No.9.
106. LaKind JS, Jenkins RA, Naiman DQ, Ginevan ME, Graves CG, Tardiff RG. Use of environmental tobacco smoke constituents as markers for exposure. *Risk Anal* 1999;19:359–373. [PubMed: 10765410]
107. National Research Co. Environmental Tobacco Smoke. Measuring Exposure and Assessing Health Effects. National Academy Press; Washington, DC: 1986.
108. Tang H, Richards G, Benner CL, et al. Solanesol: A tracer for environmental tobacco smoke particles. *Environ Sci Technol* 1990;24:848–52.
109. Seeman JI. Possible role of ammonia on the deposition, retention, and absorption of nicotine in humans while smoking. *Chem Res Toxicol* 2007;20:326–43. [PubMed: 17316028]
110. Tucker SP, Pretty JR. Identification of oxidation products of solanesol produced during air sampling for smoke by electrospray mass spectrometry and HPLC. *Analyst* 2005;130:1414–24. [PubMed: 16172668]
111. *Cancer Biomarkers* – the promises and challenges of improving detection and treatment. Institutes of Medicine, of the National Academies. The National Academies Press; Washington, DC: 2007. p. 236
112. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nat Rev Cancer* 2003;3:733–44. [PubMed: 14570033]
113. Shin HJ, Sohn HO, Han JH, et al. Effect of cigarette filters on the chemical composition and *in vitro* biological activity of cigarette mainstream smoke. *Food Chem Toxicol* 2009;47:192–7. [PubMed: 19027817]
114. Hatsukami DK, Joseph AM, Lesage M, et al. Developing the science base for reducing tobacco harm. *Nicotine Tob Res* 2007;9(Suppl 4):S537–53. Review. [PubMed: 18067031]
115. Church TR, Anderson KE, Caporaso NE, et al. A prospectively measured serum biomarker for a tobacco-specific carcinogen and lung cancer in smokers. *Cancer Epidemiol Biomarkers Prev* 2009;18:260–66. [PubMed: 19124507]
116. Lowe FJ, Gregg EO, McEwan M. Evaluation of biomarkers of exposure and potential harm in smokers, former smokers and never-smokers. *Clin Chem Lab Med* 2009;47:310–20.
117. US Patent 258,255. Cigarette. May 23, 1882. Awarded to Henry H. Schleber, Rochester, NY. Retrieved on 09/02/2009 from
118. “The History of Filters.” Retrieved on 09/02/2009 from
119. CHAPTER 2 - Cigarette Components Ltd and the Bunzl and Filtrona Groups Historical Development. Retrieved on 09/02/2009 from
120. Parliament (cigarette). Retrieved from Wikipedia on 09/02/2009 at
121. Viceroy (cigarette). Retrieved from Wikipedia. on 09/02/2009 at
122. History of Cigarettes and Smoking. Retrieved on 09/02/2009 from
123. Browne, CL. The Design of Cigarettes. Vol. 3. Charlotte, NC: Hoechst Celanese Corporation; 1990.
124. Borio G. The tobacco timeline. Retrieved on 09/04/2009 from.
125. Longo WE, Rigler MW, Slade J. Crocidolite asbestos fibers in smoke from original Kent cigarettes. *Cancer Res* 1995;55:2232–35. [PubMed: 7757969]
126. Lark (cigarette). Retrieved from Wikipedia on 09/02/2009 from
127. Miller L, Monahan J. Reports to Consumers on American Cigarettes. Reader’s Digest 1954:1–6.
128. Dunn WL Jr. A study of the effect of lip occlusion of air holes on main stream delivery in air diluted cigarettes. Bates Number 1001892531–1001892534. Retrieved 09–09–09.
129. Correspondence. To: W. L. Dunn. From: L. Wilson, Subject: Cigarette Measurements. Purpose: Study designed to determine the extent to which a smoker places the filter in his mouth. Bates Number 1003295399.
130. Pillsbury, HC.; Bright, CC.; O’Connor, KJ.; Irish, FW. Tar and nicotine in cigarette smoke. 82nd Annual Meeting of the Association of Official Analytical Chemists; 1968 Oct 14–17; Washington D.C.

131. O'Connor RJ, Hammond D, McNeill A, King B, Kozlowski LT, Giovino GA, Cummings KM. How do different cigarette design features influence the standard tar yields of popular cigarette brands sold in different countries? *Tob Control* 2008 Sep;17(Suppl 1):i1–5. [PubMed: 18768453]
132. Kozlowski LT, O'Connor RJ. Cigarette filter ventilation is a defective design because of misleading taste, bigger puffs, and blocked vents. *Tob Control* 2002;11:i40–i50. [PubMed: 11893814]
133. Green CR, Conrad FW, Bridle KA, Borgerding MF. A liquid chromatography procedure for analysis of nicotine on cellulose acetate filters. *Beitr Tabakforsch Int* 1985;13:11–6.
134. Pauly JL, Mepani AB, Lesses JD, Cummings KM, Streck RJ. Cigarettes with defective filters marketed for 40 years: what Philip Morris never told smokers. *Tob Control* 2002;11(Suppl 1):i51–61. [PubMed: 11893815]
135. Pauly JL, Waight JD, Paszkiewicz GM. Tobacco flakes on cigarette filters grow bacteria: a potential health risk to the smoker? *Tob Control* 2008;17:i49–52. [PubMed: 18768459]
136. Pauly JL, Smith LA, Rickert MH, Hutson A, Paszkiewicz GM. Review: Is lung inflammation associated with microbes and microbial toxins in cigarette tobacco smoke? *Immunol Res.* 2009 in press.
137. Carpenter CM, Wayne GF, Pauly JL, Koh HK, Connolly GN. New cigarette brands with flavors that appeal to youth: tobacco marketing strategies. *Health Aff (Millwood)* 2005;24:1601–10. [PubMed: 16284034]
138. Richard C. New Camel brand contains crushable capsule. *Winston-Salem Journal.* 2008 May 5;
139. Shepperd CJ, Eldridge AC, Mariner DC, et al. A study to estimate and correlate cigarette smoke exposure in smokers in Germany as determined by filter analysis and biomarkers of exposure. *Reg Toxicol Pharm* 2009;55:97–109.

Figure 1.
View of filter stains from cigarettes that had been smoked with filter ventilation holes that had not been blocked (left panel) and had been blocked (right panel).

Table 1

Milestones of cigarette filter development and published papers describing cigarette filter-based assays as proxies for smoking behavior and exposure

Year	Discovery
1860 to 1920	The concept of cigarette filters was formulated; the intent was to keep tobacco particles from entering the mouth. Initially, the filter was a truncated cigarette holder that contained a plug of cotton. (117)
1927	Boris Aivaz files a patent for a cigarette filter made of crepe paper with or without cellulose wadding. Two years later, he promoted the idea to filter maker Filtrona of Vienna. (118,119)
1931	<i>Parliament</i> (Benson and Hedges) cigarette was introduced as a premium priced filtered cigarette. The filter consisted of a cardboard mouthpiece with a tuft of cotton. It was considered the first major filter tip cigarette in the U.S. (120)
1936	<i>Viceroy</i> originated in the U.S. as the world's first cork-tipped filter cigarette. In 1952 it was the first brand to add a cellulose acetate filter, establishing a new industry standard. (121)
1939	"Brown and Williams introduces <i>Viceroy</i> , the first national brand to feature a filter of cellulose acetate. Advertising increases the use of physicians to counter the claims that cigarettes are a major health problem." (122)
1939	Machinery was developed that bound the cigarette filter to the tobacco column, thus facilitating high-speed production of filter cigarettes. Notwithstanding, filter cigarettes generated little interest and contributed very little to the market.
1940	Cigarettes were smoked almost exclusively by men. Filters were promoted as a novelty item to attract female smokers to grow sales. (123)
1952	Lorillard introduces <i>Kent</i> with a 'Micronite Filter' that "offers the greatest health protection in cigarette history." The filter was made of asbestos and was discontinued four years later. (124,125)
1954	RJ Reynolds introduces <i>Winston</i> filter cigarettes, but promotes the taste benefit, not health risk reduction.
1956	Fluorescent tars in smoke condensate of mechanically smoked cigarettes stained different types of cells as observed with a fluorescent microscope. This observed fluorescence of tobacco tar became the basis for subsequent assays, reported in 1960 (see below), of cigarette filter tar-trapping efficiency. (18)
1960	Cigarette filters efficiency defined by photofluorometry. (20)
1963	Liggett and Myers introduced the <i>Lark</i> with a trademark charcoal filter in an effort to halt a five- year downward drift in sales. The distinguishing feature of the brand, both in terms of physical characteristics and taste, was the three-piece "Keith" filter, the middle section of which contains small charcoal granules, reportedly reducing the harmfulness of the cigarette's smoke. (126)
1964	Consumers seek facts about filter-tip cigarettes, "safer" cigarettes, lung cancer and the dilemma of the "problem smoker." (127)
1967	Philip Morris scientists express concern that smokers could block filter ventilation holes with lips while smoking. (128,129)
1968	CORESTA methods are described for determining alkaloid (nicotine) retained by the cigarette filter. Nicotine content of steam condensate from the filter was defined by spectrophotometry. Spectro- photometric method reported the following year for measuring tar and nicotine in cigarette smoke captured onto a Cambridge pad. (130)
1970	Filters are made with vents that permit air to be introduced into mainstream smoke. This design feature generates misleadingly lower tar yields recorded by smoking machines, yields a lighter and milder taste that may be misinterpreted by the smoker as being less dangerous and

Year	Discovery
	for very heavily ventilated cigarettes, may lead to the smoker to compensatory smoking behavior. (131,132)
1973 (estimated)	Factors influencing the retention of smoke constituents in cigarettes with cellulose filters with and without activated carbon were reported by scientists in Switzerland.
1973	Scientists at the Tennessee Eastman Company describe a method for measuring the elution of nicotine and total particulate matter from a cigarette filter. The technique used ¹⁴ C-labeled nicotine or ¹⁴ C randomly labeled tobacco. (26)
1976	The amount of nicotine entering the mouth of a smoker, defined as the mouth-level exposure, was estimated from a determination of the amount of nicotine trapped in the filter of each cigarette smoked. The results indicated a substantial variation in mouth-level exposure for the subjects studied, even among smokers of cigarettes that deliver similar amounts of nicotine when smoked on a machine under conditions that were programmed to mimic human smoking. (27)
1977	A method is described for the quantitative analysis of cigarette tars using fluorescence spectroscopy. (28)
1980	Almost all cigarettes sold have filters (93% market share, non-filter cigarettes, 7% market share).
1980	An automated method of measuring FTC (Federal Trade Commission) tar of low delivery cigarettes is described. 2-propanol was used to extract the total particulate matter (TPM) from Cambridge pads. The measurements were taken for extracts excited at 475 nm and emission recorded at 520 nm. (29) The same year, a spectrophotometric method was described for measuring the efficiency of cigarette filters. (30)
1980	A spectrophotometric method was described for measuring the filtration efficiency of cigarette filters. TPM on the cigarette filters and Cambridge pad was directly proportional to the absorbance of the methanol solution measured at 310 nm. (30)
1980	Reports of studies that were undertaken to measure temporal patterns of mouth level nicotine exposure and smoking rates by subjects in a natural setting. The results showed that there was great variability in individual smoking patterns over the day. (31)
1980	Studies showed that smokers of low-yield, ventilated-filter ('less-hazardous') cigarettes sometimes defeat the purpose of the smoke-dilution holes by occluding the holes unintentionally with the fingers or lips, or intentionally with tape. (32) Other ventilation hole blocking studies have been presented. (35)
1982	A technique is described that enables individuals to detect the number of puffs taken on a filter cigarette. With the proposed method, the "color" of spent filters after smoking is compared to a color scale that simulates the appearance of the filters exposed to low-, standard-, or high-yield smoking regimens. (33)
1985	Liquid chromatography procedure established for the analysis of nicotine on cellulose acetate filters. (133)
2002	Health concern is expressed for material released from the cigarette filter into mainstream smoke. These include tar-coated cellulose acetate filter fibers and particles, carbon granules from charcoal cigarettes (134), asbestos from the filters of Kent "Micronite" cigarettes, and, more recently, microbes and microbial toxins of tobacco flake. (135,136)
2003	Philip Morris introduces Marlboro <i>UltraSmooth</i> characterized as new cigarettes with a new technology that allows the flavors and nicotine through a new carbon filter so as to provide a smooth taste and nicotine, but with potentially less exposure to the carcinogens of conventional cigarettes. The cigarette, characterized as a potential reduced exposure product (PREP), failed to gain significant consumers' acceptance and was withdrawn in 2008. (94)
2005	RJ Reynolds introduces new cigarette brands with flavors in the filter to appeal to youths. (137)

Year	Discovery
2006	Comparison of smoke exposure as defined by analysis of cigarette filter, saliva and urine. (72)
2006	Validation obtained for methods to determine consumer smoked cigarette yields from cigarette filter analysis. (73)
2008	Spectrofluorometric method established for measuring smoke particulate matter on cigarette filters and Cambridge pads. (86)
2008	Camel <i>Crush</i> is a R. J. Reynolds cigarette product - a full flavor cigarette containing a capsule in the filter that, when crushed, releases a liquid which causes the smoke to be menthol flavored. (138)
2008	Comparative studies of different filter designs define the effect of charcoal containing cigarette filters on gas phase volatile organic compounds in cigarette smoke. (93–98)
2009	Polzin and co-workers report expand the technologies to provide a lower cost high-throughput method for estimating smokers' mouth-level of exposure to select mainstream smoke constituents from discarded filter butts. (88)
2009	Investigators at BAT report the results of studies of to estimate and correlate cigarette smoke exposure in smokers in Germany as defined with the use of spent filters and biomarkers of exposure. (139)

Table 2

Results of literature search on relevant filter-related studies by source

Literature source	Number of papers identified	Corresponding reference citation
Peer-reviewed scientific papers identified in <i>PubMed</i> or <i>Scopus</i>	42	19, 21, 23, 25, 27, 29, 39, 41, 42, 44, 47, 50, 51, 54, 55, 57, 58, 61, 63, 66, 71, 73, 75, 77, 80, 85, 86, 88, 89,
Patents	1	52
Dissertations	1	46
Other documents	6	24, 40, 48, 56, 62, 70
Abstracts and presentations from scientific meetings	20	18, 22, 28, 43, 49, 53, 59, 60, 64, 65, 67, 69, 74, 78, 79, 81, 83, 87
Total	70	

Table 3
Summary of advantages and disadvantages of five different cigarette filter-based assays

	Visual Inspection	Digital imaging	Filter particulates	Filter nicotine	Filter solanesol
Key Reference(s)	<ul style="list-style-type: none"> Kozlowski <i>et al.</i>, 1980 (32) Kozlowski <i>et al.</i>, 1982 (33) Pillitteri <i>et al.</i> 1994 (42) 	<ul style="list-style-type: none"> O'Connor <i>et al.</i>, 2005 (63) O'Connor <i>et al.</i>, 2007 (80) 	<ul style="list-style-type: none"> Paszkiwicz & Pauly, 2008 (86) 	<ul style="list-style-type: none"> St. Charles <i>et al.</i>, 2006 (72) Sheppard <i>et al.</i>, 2006 (73) Sheppard <i>et al.</i>, 2009 (139) 	<ul style="list-style-type: none"> Watson <i>et al.</i>, 2004 (55, 57) Polzin <i>et al.</i>, 2009 (88)
Basic methodology	Human raters inspect filter for color intensity compared to standards; and human raters estimate percentage of staining reaching outer edge of filter	Computer software segments image of mouth end of filter into edge and center and computes average color scores for each portion	Extraction of TPM from filter with solvent (alcohol) or digestion (DMSO) of filter; followed by ultraviolet spectrofluorometry	Extraction of nicotine followed by quantitation by gas chromatography (GC) or high performance liquid chromatography (HPLC)	Extraction of solanesol followed by quantitation by liquid chromatography and mass spectrophotometry (LC/MS)
Advantages of method	Conceptually simple. Does not require chemistry lab	Conceptually simple. Does not require chemistry lab; Color features are objective and can be standardized	Technically simple assay; known fluorescence standards available	Conceptual link to exposure; data on relationship to nicotine intake	Stable, high molecular weight target -- newer methods less complex; data linking to NNK exposure
Disadvantages of method	Requires training of raters; and limits scope of measurement (vent blocking; puff count)	Limited relationship to exposure biomarkers; currently labor intensive	No data on relationship to exposure biomarkers	Nicotine semi volatile; only papers from BAT	LC/MS equipment needed. Expensive, and relatively time intensive

Table 4

Summary of conclusions, research gaps and opportunities related to cigarette filter-based assays

Conclusions from literature	<ul style="list-style-type: none"> • Sufficient data exists to link filter-based chemical measures to machine-measured yields of tar and nicotine • Tar eluted from filters or in chemical digest of filters can be used to estimate the efficiency of the filter for trapping tobacco smoke solids • Digital inspection of filters can be used as indicators of smoking behaviors such as filter vent blocking, number of puffs taken, and total volume drawn • Limited data suggests a correlation between solanesol and nicotine measured in filters and exposure biomarkers in smokers, although there is an inherent upper limit to the relationship between the filter assay and a biomarker
Key research gaps and opportunities	<ul style="list-style-type: none"> • There is an absence of head-to-head comparison of the different assays in the published literature, so there is an absence of a scientific basis for determining which approach is superior and under what conditions • Research is required to assure that a proposed assay is applicable across different filter designs (e.g., fiber type and size, charcoal, ion resins and flavor pellets) • Data on the loss rate for nicotine from stored filters would be desirable, as would data on stability under different storage conditions, such as room temperature, refrigerated (4° C), frozen (–20° C), and ultralow (–70° C) • Linkage of filter-based assays to biomarkers of exposure other than nicotine and with biomarkers of biological effect is needed to test whether filter-based assays can serve as proxy measures of mouth-level exposure